REMARKS

In the instant amendment, claims 2 and 7 have been amended. Claims 1-12 are pending and under consideration.

I. AMENDMENTS TO THE CLAIMS

The amendments to claims 2 and 7 are fully supported by the specification and claims as filed. No new matter has been added. No amendment fee is believed to be due.

II. REJECTION OF CLAIMS 1-5 UNDER 35 U.S.C. § 102(b)

Claims 1-5 stand rejected under 35 U.S.C. § 102(b), allegedly as being anticipated by Benner (U.S. Patent No. 5,432,272). The Patent Office alleges that Benner teaches the methods recited in claims 1-5. Applicants respectfully traverse the rejection of claims 1-5.

A single prior art reference anticipates a patent claim if it expressly or inherently describes *each and every limitation* set forth in the patent claim. *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295, 63 USPQ2d 1597, 1599 (Fed. Cir. 2002) (emphasis added). Applicants respectfully submit that Benner does not teach each and every limitation of any one of claims 1-5.

The Patent Office recites claim 1 in its entirety and alleges in a conclusory manner that Benner at Example 2 and at Column 2, line 61, to Column 3, line 35, teaches the method of claim 1. *See* Office Action of September 16th, page 2. Claim 1 recites a method of identifying a coded test unit in a plurality of coded test units comprising the step of: contacting the coded test unit with a decoding oligonucleotide comprising an orthogonal nucleobase under conditions in which the decoding oligonucleotide produces a detectable hybridization signal sufficient to distinguish the coded test unit from the remainder of the plurality of coded test units. The Patent Office has not explained where Benner teaches the elements of instant claim 1, for instance, where the recited "plurality of coded test units" is to be found, or the step of "contacting the coded test unit with a decoding oligonucleotide . . . under conditions in which the decoding oligonucleotide produces a detectable hybridization signal sufficient to distinguish the coded test unit from the remainder of the plurality of coded test units" as recited in claim 1. Indeed, Benner does not teach each and every element of claim 1.

Actually reading the sections of Benner cited by the Patent Office demonstrates that Benner does not teach each and every element of claim 1. For example, Benner at Example 2 teaches the enzyme-catalyzed synthesis of a nucleic acid strand in which iso-G is

incorporated opposite of the iso-C position the template strand. To illustrate, Example 2 of Benner begins with a description of the synthesis of nucleic acid templates, including two different templates that contain iso-C:

> The isoC-isoG Base Pair
>
> Protected d-iso-C suitable as a building block for the chemical synthesis of DNA was synthesized by direct extensions of standard methods. . . . N^2 -benzoyl-5'-dimethoxytrityl-d-iso-C diisopropyl phosphoramidite, used directly in machine-DNA synthesis, was synthesisized from d-iso-C by the general procedure of Atkinson and Smith . . . . This was incorporated into two templates, and three other templates containing only natural bases were synthesized for use as standards and controls.

(citations deleted). Here the "plurality of coded test units" recited in claim 1 is not taught, nor the step of "contacting the coded test unit with a decoding oligonucleotide . . . under conditions in which the decoding oligonucleotide produces a detectable hybridization signal sufficient to distinguish the coded test unit from the remainder of the plurality of coded test units" as recited in claim 1.

Example 2 of Benner continues by describing the annealing of a primer to the templates:

> An 8-mer primer was annealed to the appropriate templates (FIG. 5) to provide a double stranded binding site for the Klenow fragment of DNA polymerase I (*E. coli*), followed by a single stranded coding region containing d-iso-C flanked only by purine nucleotides. Alternatively, different templates (FIG. 5) were annealed to an 18-mer to give the double stranded promoter region required by T7 RNA polymerase, followed by a single stranded coding region containing d-iso-C. In all of the templates, a unique A at the end of the coding strand was included to direct the incorporation of radiolabelled T or U and ribo- and deoxyribo-iso-GTP's.

Although Benner refers to a single-stranded template portion of the primer/template hybrid as a coding region, the "plurality of coded test units" recited in claim 1 is not taught, nor the step of "contacting the coded test unit with a decoding oligonucleotide . . . under conditions in which the decoding oligonucleotide produces a detectable hybridization signal sufficient to distinguish the coded test unit from the remainder of the plurality of coded test units" as recited in claim 1.

Next, Example 2 of Benner describes conditions for 8-mer primer extension with the Klenow fragment and resulting products of extension:

> The reactions with the Klenow fragment were conducted by incubating template/primer, polymerase, and a mixture of the required dNTPs including (α-^{32}P)TTP. Following incubation, the products were analyzed by gel electrophoresis and autoradiography. With primed templates containing iso-C, full length product was obtained only with d-iso-GTP

> present in the incubation mixture. The presence of iso-G at the correct position in the product oligonucleotide was positively established by a "nearest neighbor" analysis . . . and by the "minus" sequencing method. . . . . As expected, in an incubation of a primed template containing T with dATP and the required dNTPs in the absence of d-iso-GTP, full length product was observed only to the extent anticipated by the fact that a small amount (15%) of dUTP was present in the template due to the deamination of iso-C (vide supra).

(citations deleted). Again, the "plurality of coded test units" recited in claim 1 is not taught, nor the step of "contacting the coded test unit with a decoding oligonucleotide . . . under conditions in which the decoding oligonucleotide produces a detectable hybridization signal sufficient to distinguish the coded test unit from the remainder of the plurality of coded test units" as recited in claim 1.

The concluding two paragraphs of Benner's Example 2 discuss an observed undesirable infidelity between iso-G and T and evidence that T7 RNA polymerase activity, similarly to that of the Klenow fragment, incorporated iso-G into a newly synthesized strand opposite iso-C in the template strand:

> Infidelity between iso-G and T was anticipated due to the known existence of a minor "phenolic" tautomer of iso-G in addition to the major N_1-H tautomer (. . . the possibility that this minor tautomer could form a Watson-Crick base pair with T was recognized on theoretical grounds[)]. In fact, incubation of a primed template containing T in place of d-iso-C with the required dNTPs and d-iso-GTP did yield a significant amount of full length product. This result strongly suggests that polymerases synthesize a base pair between T and the "phenolic" tautomer of iso-G. This fact diminishes the value of the base pair between iso-G and iso-C for many (but not all[)] applications.
>
> In analogous experiments, T7 RNA polymerase was shown to accept the new base pair. Incubation of a template (FIG. 5) possessing the T7 promoter with the required NTPs yielded more full length product in the presence iso-GTP than in its absence. Sequencing of the RNA transcript positively established the presence of iso-G in the product at the expected position.

(citations deleted). Here too, the "plurality of coded test units" recited in claim 1 is not taught, nor the step of "contacting the coded test unit with a decoding oligonucleotide . . . under conditions in which the decoding oligonucleotide produces a detectable hybridization signal sufficient to distinguish the coded test unit from the remainder of the plurality of coded test units" as recited in claim 1.

In addition to Example 2 of Benner, discussed above, the Patent Office also cited Benner at Column 2, line 61 to Column 3, line 35 as teaching the method of claim 1. The elements of claim 1 that are not taught by Benner in Example 2 are certainly not to be found

in Benner at Column 2, line 61 to Column 3, line 35. To illustrate, Benner begins the section at Column 2, line 61 as follows:

> Many of the limitations that arise from the existence of only four natural nucleoside bases, joined in only two types of base pairs via only two types of hydrogen bonding schemes, could be overcome were additional bases available that could be incorporated into oligonucleotides, where the additional bases presented patterns of hydrogen bond donating and accepting groups in a pattern different from those presented by the natural bases, and therefore could form base pairs exclusively with additional complementary bases. The purpose of this invention is to describe compositions of matter containing these additional bases, and methods for their incorporation into analogs of oligonucleotides.

This paragraph of Benner explains the purpose of Benner's invention to describe compositions of matter containing bases other than A, C, G, and T, and methods for their incorporation into analogs of oligonucleotides. Clearly, the "plurality of coded test units" recited in claim 1 is not taught in this paragraph of Benner, nor the step of "contacting the coded test unit with a decoding oligonucleotide . . . under conditions in which the decoding oligonucleotide produces a detectable hybridization signal sufficient to distinguish the coded test unit from the remainder of the plurality of coded test units" as recited in claim 1.

The next paragraph of Benner continues with the theoretical underpinnings of Benner's invention:

> In the naturally-occurring base pairs, the pyrimidines components present an acceptor-donor-acceptor (T) or a donor-acceptor-acceptor (C) pattern of hydrogen bonds to a purine on an opposite strand. This invention is based on the fact that bases with other patterns of hydrogen bond donating and accepting groups can fit the standard Watson-Crick geometry. For example, FIG. 2 discloses four base pairs that have still different patterns, an acceptor-acceptor-donor pattern for iso-C, and donor-acceptor-donor pattern for K. Bases, pairing schemes, and base pairs that have hydrogen bonding patterns different from those found in the AT and GC base pairs are here termed "non-standard". Although not found (so far) in Nature, the non-standard base pairs [(]shown in FIG. 2) apparently can fit into the DNA ladder in a standard Watson-Crick duplex.

Here, the "plurality of coded test units" recited in claim 1 is not taught , nor the step of "contacting the coded test unit with a decoding oligonucleotide . . . under conditions in which the decoding oligonucleotide produces a detectable hybridization signal sufficient to distinguish the coded test unit from the remainder of the plurality of coded test units" as recited in claim 1. This section of Benner concludes with

> Further, the patterns of hydrogen bonds in these non-standard pyrimidines are different from each other, and different from those in the natural pyrimidines T and C. This suggested that in an enzyme-catalyzed polymerization, it might be possible for each non-standard pyrimidine to

> recognize uniquely its complementary purine with high fidelity. Thus, it should be possible to make copies of a DNA molecule containing all 12 bases simply by following an expanded set of Watson-Crick rules: A pairs with T, G pairs with C, iso-C pairs with iso-G, and K pairs with X, H pairs with J, and M pairs with N (FIG. 2). In other words, it should be possible to have a genetic alphabet with twelve bases instead of four.

This last paragraph, just as with the entirety of Benner's disclosure, does not teach the "plurality of coded test units" recited in claim 1, nor the step of "contacting the coded test unit with a decoding oligonucleotide . . . under conditions in which the decoding oligonucleotide produces a detectable hybridization signal sufficient to distinguish the coded test unit from the remainder of the plurality of coded test units" as recited in claim 1.

Applicants respectfully submit that the Patent Office has failed to establish that Benner teaches *each and every limitation* set forth in the claim 1, and therefore, the Patent Office has not presented a case for anticipation of claim 1 under 35 U.S.C. § 102(b) in view of Benner.

Moving on to the next allegation made by the Patent Office, the Patent Office recites claim 2 alleging that Benner at Example 2 and at Figure 5 teaches the method of claim 2. *See* Office Action of September 16th, page 3. The Patent Office provides no additional comment in this regard, rendering it difficult to understand how the Patent Office arrives at its conclusion. Applicants respectfully submit that the Patent Office has found no teaching in Benner for its assertion against claim 2.

Claim 2 recites a method for decoding a plurality of coded test units comprising the steps of identifying a first molecule in the plurality of coded test units according to the method of Claim 1, and identifying a second molecule in the plurality of coded test units according to the method of Claim 1. Not one of the passages quoted from Example 2 of Benner, presented above, teach the first step of claim 2 identifying a first molecule in the plurality of coded test units according to the method of claim 1. Certainly, Example 2 does not teach identifying a second molecule as in the second step of claim 2. Even the additional teaching of Benner's Figure 5 adds nothing to Patent Office's argument. Figure 5 depicts the following:

> Figure 5: Templates used in the Examples
>
> Templates for T7 RNA polymerase
>
> d-5′-GATTTTGA
> d-3′-CTAAAACTGGKGA
>
> d-5′-GATTTTGA
> d-3′-CTAAAACTGG*iso*-CGA
>
> d-5′-GATTTTGA

d-3′-CTAAAACTGGTGA

d-5′-GATTTTGA
d-3′-CTAAAACTGGCGA

Templates for DNA polymerase

d-5′-TAATACGACTCACTATAG
d-3′-ATTATGCTGAGTGATATCGCGGCKCGA

d-5′-TAATACGACTCACTATAG
d-3′-ATTATGCTGAGTGATATCGCGGC*iso*-CCGA

d-5′-TAATACGACTCACTATAG
d-3′-ATTATGCTGAGTGATATCGCGGCCCGA

Applicants respectfully invite the Patent Office to indicate where in Example 2 and/or in Figure 5 of Benner does Benner disclose the method of instant claim 2, where the recited "plurality of coded test units" is to be found, or the first step of "identifying a first molecule in the plurality of coded test units according to the method of Claim 1," or the second step of "identifying a second molecule in the plurality of coded test units according to the method of Claim 1." With all due respect, Applicants submit that the Patent Office cannot, since Benner does not teach or suggest a method as in claim 2.

On page 6 of the September 16th Office Action, the Patent Office misconstrues Applicants' previous response as arguing that Benner teaches an additional step to claim 2. Upon re-reading, the Patent Office will note that Applicants merely submitted that Benner does not teach or suggest the first or second step of claim 2.

The Patent Office has not specifically addressed dependent claims 3 and 4.

In the Patent Office's next allegation, the Patent Office appears to address claim 5 by stating that Benner teaches a method, wherein the coded test unit is coded with a decoding oligonucleotide independently comprising an orthogonal nucleobase selected from iso-C, iso-G, K, X or H, and citing Column 3, lines 6-35 of Benner. Benner at Column 3, lines 6-35 does not teach each and every element of the method of claim 5. Dependent claim 5 recites the method of Claim 1, 2, 3 or 4 wherein the orthogonal nucleobase is iso-C, iso-G, K, X or H. The passage from Benner cited by the Patent Office merely teaches base pairing between non-standard base pairs of iso-C with iso-G, K with X, H with J and M with N, as follows:

> In the naturally-occurring base pairs, the pyrimidines components present an acceptor-donor-acceptor (T) or a donor-acceptor-acceptor (C) pattern of hydrogen bonds to a purine on an opposite strand. This invention is based on the fact that bases with other patterns of hydrogen bond donating and accepting groups can fit the standard Watson-Crick geometry. For example, FIG. 2 discloses four base pairs

> that have still different patterns, an acceptor-acceptor-donor pattern for iso-C, and donor-acceptor-donor pattern for K. Bases, pairing schemes, and base pairs that have hydrogen bonding patterns different from those found in the AT and GC base pairs are here termed "non-standard". Although not found (so far) in Nature, the non-standard base pairs [(]shown in FIG. 2) apparently can fit into the DNA ladder in a standard Watson-Crick duplex.
>
> Further, the patterns of hydrogen bonds in these non-standard pyrimidines are different from each other, and different from those in the natural pyrimidines T and C. This suggested that in an enzyme-catalyzed polymerization, it might be possible for each non-standard pyrimidine to recognize uniquely its complementary purine with high fidelity. Thus, it should be possible to make copies of a DNA molecule containing all 12 bases simply by following an expanded set of Watson-Crick rules: A pairs with T, G pairs with C, iso-C pairs with iso-G, and K pairs with X, H pairs with J, and M pairs with N (FIG. 2). In other words, it should be possible to have a genetic alphabet with twelve bases instead of four.

(Benner, Col. 3, lines 6-35). Instant claim 5 is a method claim, and Benner does not teach each and every element of the method of claim 5. For example, the "plurality of coded test units" recited in base claim 1 is not taught in these two paragraphs of Benner, nor the step of "contacting the coded test unit with a decoding oligonucleotide . . . under conditions in which the decoding oligonucleotide produces a detectable hybridization signal sufficient to distinguish the coded test unit from the remainder of the plurality of coded test units" as recited in base claim 1. Applicants respectfully remind the Patent Office that a dependent claim incorporates all the limitations of its base claims, and the Patent Office has not established that each and every limitation of claim 1, 2, 3 or 4 have been taught by Benner (as discussed above).

For the foregoing reasons, Applicants respectfully submit that Benner does not teach or suggest each and every limitation recited in any one of method claims 1-5 in the instant application. Accordingly, Applicants kindly request the withdrawal of the rejection of claims 1-5 under 35 U.S.C. § 102(b).

III. REJECTION OF CLAIMS 6-12 UNDER 35 U.S.C. § 103(a)

Claims 6-12 stand rejected under 35 U.S.C. § 103(a), allegedly as being obvious over Benner (U.S. Patent No. 5,432,272) in view of Southern (U.S. Patent 6,054,270). The Patent Office contends that it would have been *prima facie* obvious to one of ordinary skill at the time the invention was made to substitute and combine a method of making an array of oligonucleotides on a solid support, as in Southern, with the "orthogonal nucleobase hybridization method" alleged to be taught by Benner. Applicants respectfully traverse the rejection of claims 6-12 under 35 U.S.C. § 103(a).

The legal standard of *prima facie* obviousness requires that three criteria be met: (1) the prior art, either alone or combination, must teach or suggest each and every limitation; (2) a suggestion or motivation in the cited references or in the art to modify or combine the cited references; and (3) the cited references must provide a reasonable expectation of successfully achieving the claimed invention. *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991); *In re* Wilson, 165 U.S.P.Q. 494, 496 (CCPA 1970). Applicants respectfully submit that *prima facie* obviousness has not been established since these criteria are not met.

Claim 6 recites the method of claim 1 wherein the coded test unit comprises a solid substrate. Claims 7-12 depend from claim 6. The Patent Office contends that Benner teaches the method of claim 1. The Patent Office acknowledges that Benner does not teach a method wherein the coded test unit comprises a solid substrate.

First, neither Benner nor Southern, nor both in combination, teach or suggest each and every limitation of claims 6-12. As explained in Section I above, Benner does not teach a method of using a decoding oligonucleotide comprising an orthogonal nucleobase to identify a coded test unit in a plurality of coded test units, as recited in the methods of any of claims 6-12 of the instant application. Nor does Southern teach those elements missing in Benner. Southern teaches a method of making an array of oligonucleotides on a support. Southern does not teach or suggest a method of using a decoding oligonucleotide comprising an orthogonal nucleobase to identify a coded test unit in a plurality of coded test units, as recited in the methods of any of claims 6-12 of the instant application. Since the combination of Benner and Southern does not teach or suggest each and every limitation of claims 6-12, Applicants respectfully submit that the Patent Office has not established *prima facie* obviousness. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 6-12 under 35 U.S.C. § 103(a).

Second, Applicants respectfully submit that the Patent Office has not presented a suggestion or motivation in the cited references or in the art to modify or combine the cited references. The mere fact that references could be modified or combined does not render the resultant modification or combination obvious unless the prior art also suggests the desirability of the modification or combination. *In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990); MPEP § 2143.01. The Patent Office states that "strong motivation" is provided in Southern by the statement that

> [t]his invention provides a new approach which produces both a fingerprint and a partial or complete sequence in a single analysis, and may be used directly with complex DNAs and populations of RNA without the need for cloning

(page 7 of the September 16th Office Action quoting column 1, lines 30-33 of Southern). Applicants respectfully submit that this sentence quoted from Southern does not in any way refer to coded test units (which are not taught or suggested in Southern), or refer to compositions and methods of preparing nucleic acid compositions described by Benner, and therefore does not suggest or motivate one of skill in the art to modify Southern's invention or combine it with what Benner has taught. Indeed, this quote from Southern is the advantage that Southern supplies for using Southern's own invention.

The Patent Office states that further motivation is provided by Benner since Benner states, "it might be possible for each non-standard pyrimidine to recognize uniquely its complementary purine with high fidelity" (page 7 of the September 16th Office Action quoting column 3, lines 26-28 of Benner). This statement from Benner is the rationale Benner gives for developing his own invention. It is not a suggestion to modify Benner's invention or combine it with Southern's invention.

While the Patent Office has quoted reasons for using the respective methods or compositions disclosed by Southern and Benner, the Patent Office has not explicated where the cited references suggest the desirability of the modification or combination.

Applicants therefore submit that there is no suggestion or motivation in the cited references or in the art to modify or combine the cited references, nor has one been presented by the Patent Office. A case of *prima facie* obviousness has not been made. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 6-12 under 35 U.S.C. § 103(a).

CONCLUSION

Applicants submit that the claims as presently pending meet all of the criteria for patentability and are in condition for allowance. Early notification to this effect is earnestly solicited. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

No fees, other than that for filing a Notice of Appeal, are believed due with this response. However, the Commissioner is authorized to charge any fees under 37 C.F.R. § 1.17, any underpayment of fees, or credit any overpayment to Pennie & Edmonds$_{LLP}$ U.S. Deposit Account No. 16-1150 (order no. 9584-030-999) that may be required by this Amendment and Response.

Respectfully submitted,

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